Remarks

Recombinant human protein C is generally produced by mammalian cell culture and purified by conventional chromatography techniques. When conducting production on a commercial scale, large volumes of recombinant human activated protein C (rhaPC) solution are then shipped to formulation and filing operations in sterile bags. This method for handling rhaPC is not desirable since the solution is neither stable nor easily dispensed. Additionally, this method forces a link between the schedule, scale, and site of commercial purification operations to the same parameters for the commercial formulation fill/finish operations. Applicants discovered a stable preformulation form of aPC, providing for aPC cryogranules, a process for preparing aPC cryogranules, and a process of preparing an aPC lyophilized formulation from the aPC cryogranules. This invention provides a means of processing commercial scale aPC suitable for storage, handling, and recovery.

Claims 1-8 are pending in this case.

REJECTION OF CLAIMS 42 AND 43 UNDER 35 U.S.C. § 102(b)

Claims 5 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Foster *et al.* (U.S. Patent No. 5,516,650). Since Foster does not contain cryogranules of activated protein C, Foster does not disclose all elements of the claim and, hence, does not anticipate the claimed invention. The Examiner indicates that Foster "discloses cryogranules of activated protein C, wherein the activated protein C is a human activated protein C (e.g. abstract and col. 9, lines 62 to col. 10 lines 5)." Applicants respectfully disagree with this assertion and request withdrawal of this rejection. Foster contains references to lyophilizing the protein C or activated protein C of Foster's invention. Lyophilization, also known as freeze-drying, is the process of isolating a solid substance from solution by freezing the solution and sublimating the ice under vacuum. Lyophilized material can be stored without refrigeration for long periods and can usually be rehydrated to an active state. Alternatively, activated protein C (aPC) cryogranules are generated by contacting droplets of aPC cryogranulation solution in liquid nitrogen or other freezing agents suitable for rapidly freezing the solution at temperatures from –40°C to –90°C. Discrete frozen pellets of aPC are produced during the residence time in which the solution is in contact with liquid nitrogen. The cryogranules are collected, transported to into an insulated container, and held below the glass point of the solution. These aPC cryogranules provide a stable preformulation form suitable for handling and maintaining product integrity during the manufacturing process. In fact, the Applicants disclose in the specification that "commercial freeze drying procedures

are not practical and do not solve this problem" (page 2, lines 25 through 26). Applicants also note that "large volumes of solution generated in the commercial manufacturing process renders freeze drying as an impractical technique due to the expense and the extended time needed to process the solution. Additionally, the freeze-dried protein can be fluffy, dusty, and difficult to handle as an amorphous solid powder" (page 2, lines 5 through 11). Later, these cryogranules are thawed in order to prepare the drug product. The resulting aPC solution from the thawed cryogranules is added with pharmaceutically acceptable excipients, dispensed into unit dosage receptacles, and then lyophilized. This lyophilized drug product is the form in which aPC is provided to the patient and is a later processing step that follows Applicants' current invention. Indeed, cryogranulation differs from lyophilization in many ways, including their processes and reasons for employing the given technique. With Foster only referring to lyophilization and not cryogranulation and since lyophilization and cryogranulation are two distinct processing techniques, Foster does not anticipate Claims 5 and 6 of the present invention. Therefore, Applicants respectfully request withdrawal of this rejection.

REJECTION OF CLAIMS 1-18 UNDER 35 U.S.C. § 103(a)

Applicants appreciate the Examiner's acknowledgement of joint inventorship for this application and assert that the subject matter of the various claims were commonly owned at the time any inventions covered therein were made.

Claims 1 through 8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tse *et al.* (U.S. Patent No. 5,716,645) taken with Foster *et al.* (U.S. Patent No. 5,516,650). Applicants respectfully assert that the Examiner has failed to set forth a *prima facie* case of obviousness and request withdrawal of this rejection.

In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the court defined the test for determining obviousness under 35 U.S.C. § 103: 1) determine the scope and content of the prior art; 2) ascertain the differences between the prior art and the claims at issue; 3) resolve the level of ordinary skill in the pertinent art; and 4) evaluate evidence of secondary considerations. The USPTO bears the burden of establishing a *prima facie* case. (*In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984)). In order to establish a *prima facie* case, the Examiner must show 1) some suggestion or motivation to modify the reference or to combine reference teachings (*In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988)); 2) the proposed modification had a reasonable expectation of success by a skilled artisan at the time of the invention (*Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991)); and

3) the prior art reference or combination of references must teach or suggest all limitations of the claims (*In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness.

Applicants discovered a means for providing a stable preformulation form of aPC that would facilitate handling large volumes and maintain product integrity of the solution during the manufacturing process. Applicants used cryogranulation to remedy these aPC manufacturing issues. Tse, on the other hand, teaches the use of plasma that is cryogranulated and then used to prepare a fibrinogen composition essentially free of Factor VIII. Furthermore, the Examiner notes that Tse does not mention aPC. However, the Examiner then states that "[t]he activated fibrinogen and FVIII [Factor VIII] include the specific activated protein C since they are generic." The Examiner indicates that support for this assertion is available on page 1, lines 9 through 17 of the specification. As noted in Applicants' specification, protein C is a naturally occurring anticoagulant, with the protein C enzyme system representing a major physiological mechanism of anticoagulation. Protein C plays a role in the regulation of hemostasis by inactivating Factors Va and VIIIa in the coagulation cascade. Alternatively, fibrinogen is a protein in the blood plasma that is essential for the coagulation of blood and is converted to fibrin by the action of thrombin in the presence of ionized calcium. Since fibrinogen is essential for blood coagulation while protein C and aPC are key to anticoagulation, these proteins are clearly different. More particularly, the terms "activated fibrinogen" and "Factor VIII" refer to two proteins that are completely unlike protein C and aPC. In fact, the homology between human protein C and fibrinogen as well as between human protein C and Factor VIII is low. As such, these terms are not generic terms encompassing protein C or aPC. Given these marked distinctions, Applicants respectfully assert that Tse's teachings on fibrinogen do not encompass the instantly claimed aPC.

Next, the Examiner addresses the process of preparing a lyophilized formulation of aPC after the addition of a pharmaceutically acceptable bulking agent. The Examiner directs his objections on this issue to Claims 1 through 8. Applicants respectfully assert that only Claims 7 and 8 involve a process of preparing a lyophilized formulation of aPC. Applicants wish to direct the Examiner's attention to the fact that this process includes thawing the aPC cryogranules to form a solution before proceeding to the optional addition of a pharmaceutically acceptable bulking agent and subsequent lyophilization of the solution. While Tse employs lyophilization for fibrinogen and Foster involves the use of stabilizers with protein C or aPC and subsequent lyophilization, neither reference teaches the

cryogranulation of aPC or thawing aPC cryogranules to form a solution before using a bulking agent and lyophilization. As such, neither Tse nor Foster, alone or in combination, direct the skilled artisan to Applicants' present invention which provides a means of processing commercial scale aPC suitable for storage, handling, and recovery. No evidence exists of any suggestion or motivation to modify or combine teachings from these references in order to arrive at Applicants' present invention. Additionally, Tse and Foster do not teach or suggest all limitations of the claims. Without any teachings involving cryogranulation of aPC, these references are completely unable to direct the skilled artisan to this invention. As such, these references do not render Applicants' present invention obvious. For the above-stated reasons, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants assert that the above-stated remarks obviate the noted rejections. Since Foster does not contain every element of the presently claimed invention, Foster does not anticipate Applicants' invention. Also, this invention is not obvious since neither Tse nor Foster involves cryogranulation of aPC and no suggestion or motivation to modify or combine teachings from Tse and Foster exists.

In view of these points, Applicants courteously solicit reconsideration of these rejections and passage of this case to issuance.

Respectfully submitted,

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